Efficacy and Safety of Bivalirudin During Percutaneous Coronary Intervention in Chronic Total Occlusion: A Retrospective Study

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ABSTRACT

Purpose: Bivalirudin as a thrombin inhibitor is proven to have a low risk of bleeding during percutaneous coronary intervention (PCI). Some evidence indicates comparable effectiveness and safety between bivalirudin and unfractionated heparin (UFH). Although bivalirudin during PCI offers more clinical and safety benefits to patients with chronic total occlusion (CTO), mostly via radial access, this has not been confirmed. The objective of this study was to examine the efficacy and safety of bivalirudin during percutaneous coronary intervention (PCI) in patients with CTO.

Methods: This trial used a retrospective cohort study design. Medical information from 736 patients with CTO who underwent PCI with bivalirudin or UFH at the First Affiliated Hospital of Zhengzhou University from July 2019 to September 2020 was extracted and analyzed. The primary end point was the 30-day incidence of net adverse clinical events (NACEs), and the secondary end point was the major adverse cardiovascular events (MACEs), which were related to safety and efficacy, respectively. Other end points incorporated each component of the primary outcome, target vessel revascularization, and stent thrombosis. Clinical and procedural characteristics at baseline were adjusted by using a logistic regression model.

Findings: Overall, 71.5% of patients with CTO used the radial approach. Both groups exhibited nonsignificant differences in the majority of baseline characteristics. The bivalirudin group was associated with a significant reduction in NACEs (12.9% vs 21.5%; $P = 0.002$) and major bleeding (2.5% vs 8.0%; $P = 0.001$) versus the UFH group at the end of the 30-day follow-up. The incidence of MACEs, myocardial infarction, death, stroke, stent thrombosis, and target vessel revascularization did not differ significantly between the 2 groups. Moreover, the bivalirudin group also reported a lower incidence of NACEs in the prespecified subgroups.

Implications: Bivalirudin exhibited comparative efficacy but superior safety compared with UFH among patients with CTO undergoing PCI. Chinese Clinical Trial Registry: ChiCTR2000034771. (*Clin Ther.* 2021;43:844–851.) © 2021 Elsevier Inc.

Key words: Bivalirudin, chronic total occlusion, percutaneous coronary intervention, unfractionated heparin.

INTRODUCTION

Percutaneous coronary intervention (PCI) is a sophisticated technique for treating coronary atherosclerotic heart disease. Anticoagulant agents are commonly used during PCI to prevent intraoperative thrombotic complications. The emerging anticoagulant bivalirudin has been reported to exert similar efficacy with satisfactory safety in clinical use.[1] It directly inhibits thrombin via specific binding to the catalytic sites of thrombin and anion external binding sites to prevent thrombosis, and the binding process of bivalirudin and thrombin is reversible. Anticoagulant therapy can prevent intraoperative ischemic events, but these benefits are achieved at the cost of a high risk of bleeding. Bivalirudin has been shown to decrease

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bleeding risk compared with unfractionated heparin (UFH),[1–5] with some guidelines even recommending bivalirudin as an anticoagulant with a low risk of bleeding during PCI.[6]

Chronic total occlusion (CTO) is generally defined as the complete obstruction of the forward blood flow caused by coronary atherosclerosis, and the duration of the disease often exceeds 3 months. An increasing number of patients with CTO are being identified as the use of PCI becomes more acceptable in patients, and it is reported that 15% to 30% of patients undergoing coronary angiography have CTO.[7,8] Issues during PCI remain, including longer operation time, rupture of blood vessels, and bleeding, notwithstanding the fact that PCI offers more benefits to patients with CTO. Some evidence from small-sample studies indicates that bivalirudin has similar efficacy and safety versus UFH.[9–11] This conclusion requires validation by clinical studies with larger sample size. We therefore conducted a retrospective analysis of >700 patients, with the goal of examining the efficacy and safety of bivalirudin during PCI in patients with CTO.

PATIENTS AND MATERIALS

Study Population

The essential data from 736 patients with CTO who underwent PCI and received bivalirudin or UFH intraoperatively at our hospital from July 2019 to September 2020 were collected from our electronic medical record system. Adult patients diagnosed with CTO and who accepted bivalirudin or UFH during PCI were considered eligible for further assessments of the efficacy and safety between the 2 anticoagulants.

Study Design

Use of bivalirudin or UFH was based on operators' decision. Patients in the bivalirudin group were anticoagulated intraoperatively by bolus dosing (0.75 mg/kg), a subsequent intravenous infusion dose of 1.75 mg/kg per hour (or 1.0 mg/kg per hour with a low estimated glomerular filtration rate of <30 mL/min) for a PCI procedure no more than 4 hours and an infusion dose of 0.2 mg/kg per hour for after 4 hours less than 20 hours if the procedure was longer. UFH was administered at a dose of 70 to 100 U/kg if patients had not been treated previously with glycoprotein IIb/IIIa inhibitors (GPIs); otherwise, they would be administered UFH 50 to 70 U/kg. GPI prescriptions were decided by the physician.

All participants received antiplatelet therapy at the standard dose ranges recommended (a loading dose of 300 mg of aspirin in combination with 180 mg of ticagrelor or 300–600 mg of clopidogrel) preoperatively. The incidence of clinical end points was assessed in a 1-month telephone follow-up. The J-CTO score was calculated based on the criteria of Japanese Multicentre CTO Registry.[12] This study had been registered in the Chinese Clinical Trial Registry (ChiCTR2000034771).

Study End Points

The primary outcome was net adverse clinical events (NACEs), consisting of major bleeding, all-cause death, stroke, and myocardial infarction (MI). The secondary outcome was major adverse cardiovascular events (MACEs), including all-cause death, stroke, and MI. Other outcomes encompassed each of the components of the primary outcome, stent thrombosis (ST), and target vessel revascularization. Major bleeding referred to type 3 or 5 according to the Bleeding Academic Research Consortium criteria.[13] The definitions of ST and MI were based on the Academic Research Consortium criteria and the Third Universal Definition of Myocardial Infarction, respectively.[14,15]

Statistical Analysis

All variables were examined for normal distribution. Normally distributed continuous data were analyzed by using the Student's t test and are expressed as mean (SD); otherwise, the Mann-Whitney U test was used for those non-normally distributed. The Pearson's χ^2 or Fisher's exact test was performed to assess the differences in categorical variables between groups, which are presented as frequencies or percentages. A logistic regression model was performed with the use of a forward stepwise selection approach to adjust for potential confounders, with factors including age, sex, weight, hypertension, smoking status, hyperlipidemia, diabetes mellitus, cardiac arrest, type of acute coronary syndrome, previous MI, previous PCI, peripheral vascular disease, chronic obstructive pulmonary disease, estimated glomerular filtration rate, left ventricular end-diastolic diameter, left ventricular ejection fraction, arterial access, number of diseased coronary vessel(s), treated vessel(s) per patient, median number of stents per patient, total stent length per patient, procedural success, GPI inhibitor use, and choice of $P2Y_{12}$ inhibitors. The subgroup analyses for NACEs were

Table 1. Clinic baseline characteristics. Values are given as mean (SD) unless otherwise indicated.

Characteristic	Bivalirudin (n = 326)	Unfractionated Heparin (n = 410)	*P*
Age, y	67.2 (10.9)	64.7 (11.2)	0.002
Male sex	211 (64.7%)	247 (60.2%)	0.213
Mean weight, kg	67.1 (11.3)	68.1 (12.0)	0.215
Type of acute coronary syndrome			0.624
Unstable angina	201(61.7%)	260 (63.4%)	
NSTEMI	125 (38.3%)	150 (36.6%)	
Cardiac arrest	7 (2.1%)	7 (1.7%)	0.664
Hypertension	215 (66%)	251 (61.2%)	0.186
Diabetes mellitus	112 (34.4%)	160 (39.0%)	0.192
Previous myocardial infarction	65 (19.9%)	76 (18.5%)	0.631
Previous PCI	72 (22.1%)	92 (22.4%)	0.909
Previous stroke	82 (25.2%)	87 (21.2%)	0.208
Smoking	108 (33.1%)	122 (29.8%)	0.327
Peripheral vascular disease	67 (20.6%)	104 (25.4%)	0.125
Chronic obstructive pulmonary disease	19 (5.8%)	18 (4.4%)	0.375
Hyperlipidemia	185 (56.7)	225 (54.9)	0.612
eGFR, mL/min	78.3 (23.9)	76.7 (25.8)	0.388
LVEDD, mm	49.1 (6.6)	49.0 (7.2)	0.765
LVEF, %	56.1 (9.8)	54.8 (11.0)	0.084

eGFR = estimated glomerular filtration rate; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention.

conducted with the use of a logistic regression model. A statistical significance level was set at $P < 0.05$.

RESULTS

Baseline Clinical and Procedural Characteristics

A total of 736 patients (62.2% male, 37.8% female) who were diagnosed with CTO and underwent PCI were eligible for our retrospective analysis. Among them, 326 patients received bivalirudin, and 410 accepted UFH during procedures. All baseline clinical characteristics were similar between the bivalirudin and UFH groups except for age: patients treated with bivalirudin were older than those in the UFH group. Overall, 37.4% and 62.6% of all participants, respectively, experienced non–ST-segment elevation MI and unstable angina. In terms of the underlying conditions, 63.3% reported a history of hypertension, 40.0% diabetes mellitus, and 19.2% previous MI (Table 1).

GPIs, novel $P2Y_{12}$ inhibitors, and radial access were used in 6.4%, 72.1%, and 71.5% of patients, respectively. Overall, 59.2% of patients had triple-vessel disease of coronary artery. There was no significant difference in treatment data between the 2 groups, except for the choice of arterial access, duration of procedure, and novel $P2Y_{12}$ inhibitor use. Subjects receiving UFH were more likely to received novel $P2Y_{12}$ inhibitors (75.4% vs 68.1%; $P = 0.029$) and have a longer procedure duration ($P < 0.001$), whereas the bivalirudin group had a higher frequency of the radial access being selected during procedures (76.4% vs 67.6%; $P = 0.008$) (Table 2).

Thirty-Day Clinical Outcomes

Patients receiving bivalirudin exhibited a lower rate of NACEs versus the UFH group (12.9% vs 21.5%; adjusted odds ratio, 0.51; 95% CI, 0.34–0.78; $P = 0.002$). In addition, bivalirudin significantly reduced the 30-day rate of major bleeding (2.5% vs 8.0%; adjusted odds ratio, 0.26; 95% CI, 0.12–0.58; $P = 0.001$). Nevertheless, other indices for clinical outcomes, MACEs, MI, stroke, all-cause death, ST, and

Table 2. Treatment-related data. Values are given as mean (SD) unless otherwise indicated.

Item	Bivalirudin (n = 326)	UFH (n = 410)	*P*
Arterial access			0.008
Transradial	249 (76.4%)	277 (67.6%)	
Transfemoral	77(23.6%)	133 (32.4%)	
No. of diseased coronary vessel(s)			0.954
Single-vessel disease	38 (11.7%)	48 (11.7%)	
Double-vessel disease	93 (28.5%)	121 (29.5%)	
Triple-vessel disease	195 (59.8%)	241 (58.8%)	
Treated vessels per patient			
Left main coronary artery	17 (5.2%)	33 (8.0%)	0.129
Left anterior descending artery	173 (53.1%)	223 (54.4%)	0.721
Left circumflex artery	90 (27.6%)	128 (31.2%)	0.286
Right coronary artery	143 (43.9%)	169 (41.2%)	0.471
J-CTO score*	2.0 (1.4)	2.1 (1.4)	0.730
Duration of procedure, min	149.5 (36.7)	175.0 (43.6)	<0.001
Reverse wire technique	56 (17.2%)	76 (18.5%)	0.633
IVUS	16 (4.9%)	27 (6.6%)	0.335
IABP	32 (9.8%)	34 (8.3%)	0.472
Atherectomy	10 (3.1%)	15 (3.7%)	0.660
Median no. of stents per patient	2.2 (1.0)	2.1 (1.0)	0.214
Total stent length per patient, mm	56.5 (31.4)	52.9 (28.9)	0.112
Procedural success	323 (99.1%)	407 (99.3%)	0.778
Anticoagulants other than UFH and bivalirudin	165 (50.6%)	201 (49.0%)	0.668
GPIs used	26 (8.0%)	21 (5.1%)	0.116
Choice of $P2Y_{12}$ inhibitors			0.029
Ticagrelor	222 (68.1%)	309 (75.4%)	
Clopidogrel	104 (31.9%)	101 (24.6%)	

GPIs = glycoprotein IIb/IIIa inhibitors; IABP = intra-aortic balloon pump; IVUS = intravascular ultrasonography; UFH = unfractionated heparin.
*Based on the Multicenter CTO Registry in Japan.

target vessel revascularization did not show significant differences between the 2 groups (Table 3).

Subgroup Analyses

Bivalirudin exhibited a lower 30-day prevalence of NACEs than UFH in the study subgroups, which is consistent with the overall analyses. There were nonsignificant interactions between these subgroups and treatment (Figure 1).

DISCUSSION

Bivalirudin has been commonly used as an anticoagulant during PCI. Whether it offers more benefits to patients with CTO remains unknown, although some studies have claimed comparable efficacy and safety with UFH. Our results showed that patients with CTO had a lower incidence of NACEs rather than MACEs with bivalirudin compared with those using UFH during the 30-day follow-up; the difference of low risk in major bleeding was more significant. This finding suggests the superiority of bivalirudin over UFH in bleeding risk during PCI among patients with CTO.

Despite the complexity of vascular diseases in CTO patients requiring PCI, improvements in equipment and procedural technique have pronouncedly mini-

Table 3. Clinical outcomes at 30 days.

Outcome	Total (N = 736)	Bivalirudin (n = 326)	UFH (n = 410)	Nonadjusted Odds Ratio (95% CI)	*P*	Multivariable Adjusted Odds Ratio (95% CI)	*P*
Primary end point: 30-day rate of NACEs	130 (17.7%)	42 (12.9%)	88 (21.5%)	0.54 (0.36–0.81)	0.003	0.51 (0.34–0.78)	0.002
Secondary end point: 30-day rate of MACEs	104 (14.1%)	37 (11.3%)	67 (16.3%)	0.66 (0.43–1.01)	0.055	0.67 (0.43–1.04)	0.073
All-cause death	14 (1.9%)	4 (1.2%)	10 (2.4%)	0.50 (0.15–1.60)	0.241	0.56 (0.16–2.99)	0.370
Myocardial infarction	83 (11.3%)	31 (9.5%)	52 (12.7%)	0.72 (0.45–1.16)	0.178	0.73 (0.45–1.19)	0.209
Stroke	8 (1.1%)	2 (0.6%)	6 (1.5%)	0.42 (0.08–2.07)	0.284	0.22 (0.04–1.29)	0.093
Major bleeding (BARC type 3 or 5)	41 (5.6%)	8 (2.5%)	33 (8.0%)	0.29 (0.13–0.63)	0.002	0.26 (0.12–0.58)	0.001
Access site	11 (1.5%)	2 (0.6%)	9 (2.2%)	0.28 (0.06–1.28)	0.100	0.25 (0.05–1.21)	0.084
Intracranial	2 (0.3%)	1 (0.3%)	1 (0.2%)	1.26 (0.08–20.20)	0.871	1.13 (0.07–19.1)	0.933
Gastrointestinal	12 (1.6%)	2 (0.6%)	10 (2.4%)	0.25 (0.05–1.14)	0.072	0.25 (0.05–1.13)	0.072
Genitourinary	4 (0.5%)	0 (0%)	4 (1.0%)	–	–	–	–
Pericardial	8 (1.1%)	2 (0.6%)	6 (1.5%)	0.42 (0.08–2.07)	0.284	0.50 (0.10–2.6)	0.408
Other	4 (0.5%)	1 (0.3%)	3 (0.7%)	0.42 (0.04–4.03)	0.450	0.55 (0.06–5.50)	0.610
Urgent target vessel revascularization	12 (1.6%)	4 (1.2%)	8 (2.0%)	0.62 (0.19–2.09)	0.445	0.61 (0.18–2.06)	0.425
Stent thrombosis	14 (1.9%)	3 (0.9%)	11 (2.7%)	0.34 (0.09–1.22)	0.097	0.31 (0.08–1.23)	0.096

BARC = Bleeding Academic Research Consortium; MACEs = major adverse cardiovascular events; NACEs = net adverse clinical events; UFH = unfractionated heparin.

mized the risk of treatment failure of CTO PCI.[16,17] However, the risk of ST and bleeding posed by coronary artery perforation and dissection, a long procedure time, and high doses of anticoagulation are still concerns during PCI. Hence, CTO PCI is still treated as a high-risk procedure. Growing evidence supports that thrombotic and bleeding complications are more likely to occur in patients with acute coronary syndromes.[18–20] Major bleeding that causes serious adverse consequences especially has been proven to have associations with increased MACEs, NACEs, a longer length of hospital stay, and higher mortality in

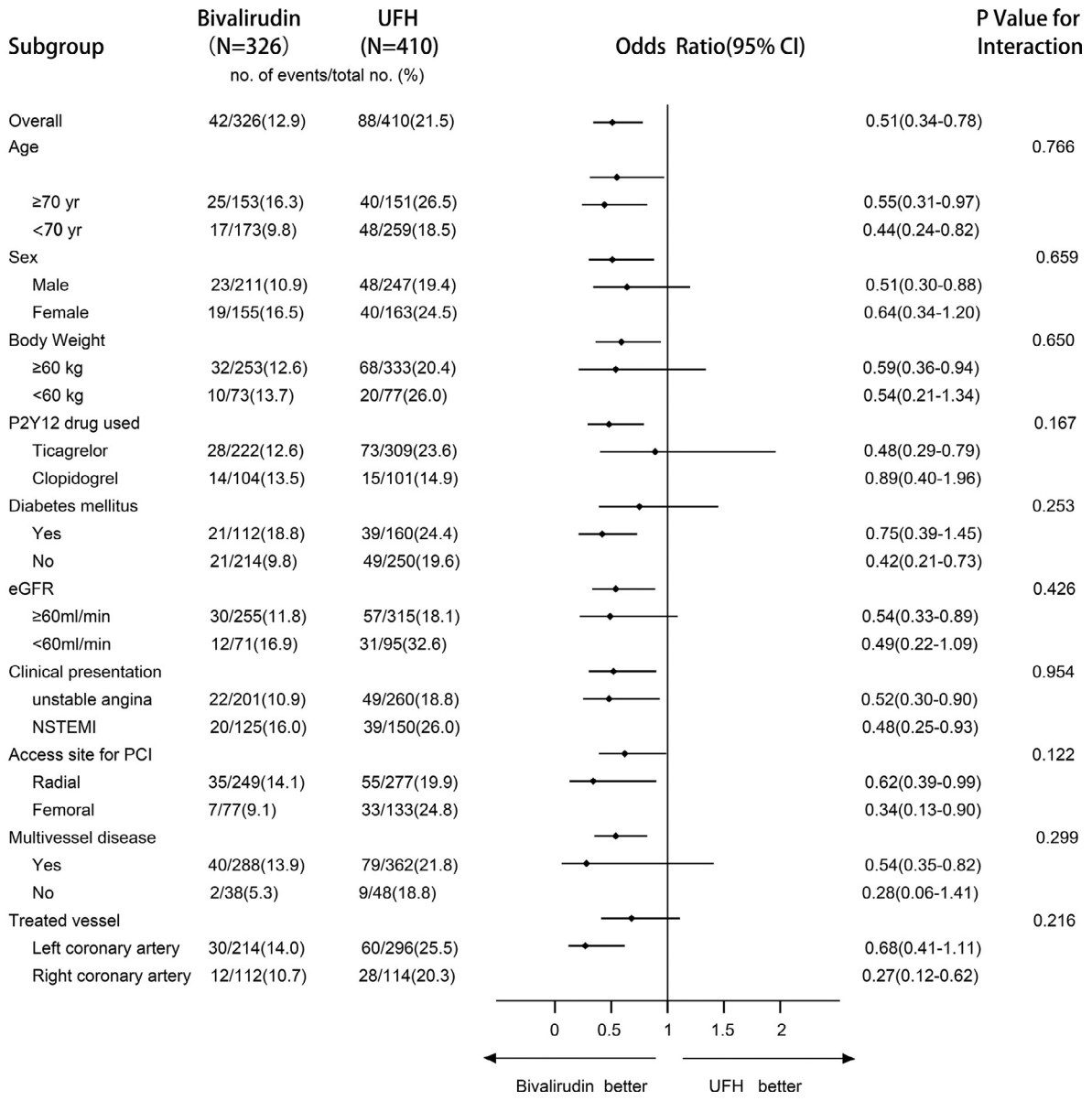

Figure 1. Subgroup analyses for the net adverse clinical events. eGFR = estimated glomerular filtration rate; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention.

the setting of PCI.[21] The rate of bleeding complications has therefore garnered great attention. In our research, bivalirudin exhibited a lower risk of major bleeding than UFH (2.5% vs 8.0%), and this result has been confirmed by the MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angio) trial[22] and the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial.[23] Our work with a larger sample size provided relatively stronger evidence that bivalirudin during PCI may be more suitable for CTO patients than UFH due to its better safety, with a lower rate of NACEs and major bleeding.

For patients with CTO, prolonged operation time and high-dose anticoagulant during the procedure with frequent use of various equipment (eg, the guidewire,

microcatheter, balloon) are the factors that differ from the PCI procedure for common lesions. Abundant collateral circulation of the coronary artery has been established in occluded vessels; in most cases, even if antegrade flow starts to recover, the perfusion pressure is lower than the retrograde blood flow because of the residual stenosis, and thus blood flow slows due to the convection of antegrade and retrograde flow. This slow blood flow in the coronary artery results in markedly reduced efficacy of bivalirudin at the site of occlusion. Its anticoagulant effect may also be weakened when coagulation function is enhanced due to the exposure of the balloon or stent to blood to some extent. All of these factors will stimulate the blood coagulation system so that the risk of ST may be higher.

Some large-sample clinical trials of patients receiving bivalirudin during PCI reported an increasing incidence of ischemic events such as ST,[3,24,25] which was inconsistent with our finding of a nonsignificant difference in the incidence of ischemic events between patients using bivalirudin versus UFH. The present study was a single-center retrospective analysis, and use of bivalirudin or UFH was at the discretion of the operator. It is possible that the more skilled operators preferred bivalirudin for personal reasons. The best results observed in the bivalirudin group might be related to operator skill. It is also possible that bivalirudin might have been preferred in more simple procedures. These factors could be the reason for the high rate of ST in the UFH group compared with the bivalirudin group. However, these factors are uncontrollable in the retrospective analysis.

There may be several other reasons for this difference. First, we adopted a sufficient dose of bivalirudin during PCI and postprocedural a full-dose infusion for 4 hours. For patients, the guidewire, microcatheter, and balloon were washed with the solution of UFH before procedures. Both factors reduced the risk of ischemic events. It has also been shown that a higher risk of major bleeding is strongly associated with the high prevalence of ischemic outcomes during PCI. Therefore, the nonsignificant difference in the incidence of ischemic events may be because of the reduced major bleeding of bivalirudin. Furthermore, a large number of patients with CTO (72.1%) received the novel antiplatelet drug (ticagrelor), which enhanced the antithrombotic effect. Finally, all patients in the present study used contemporary drug-eluting stents, which have been proven to significantly reduce the risk of ischemic events compared with first-generation drug-eluting and bare-metal stents.[26]

Nevertheless, the present study may be flawed because of the following limitations. Because this was a retrospective analysis, the type of anticoagulant agents used in this study had been selected by physicians. The present study may have highlighted potential differences in baseline and procedural characteristics between the 2 groups. In addition, further prospective clinical trials are needed to validate our findings due to the retrospective analysis. Moreover, this was a single-center study, and multicenter, large-sample randomized controlled trials are thus required to offer stronger evidence supporting the decision of a better anticoagulant regimen during PCI.

CONCLUSIONS

Bivalirudin showed comparative efficacy and better safety compared with UFH in patients with CTO undergoing PCI, which significantly lowered the 30-day incidence of NACEs and major bleeding.

DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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Drs. Yanghui Zhang and Yahao Zhang organized data and drafted the article. Dr. Chang handled all statistical analyses and graphical editing. Drs. Yan, L. Zhang, and Z. Chen extracted clinical data from the electronic medical record system. Dr. K. Chen provided interpretation of results, constructive suggestions, and revision of the manuscript. Dr. Liu was responsible for study design and article submission. All authors had full access to the data and approved the final version of this manuscript.

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